AMENDMENTS TO THE SPECIFICATION

On page 1, before the heading "FIELD OF THE INVENTION" please add the following paragraph:

-- This application is the National Stage of International Application No. PCT/EP2003/09116, filed on August 18, 3002. --

Please replace the paragraph beginning at line 22 on page 5 of the specification with the following amended paragraph:

-- The present invention is concerned primarily with the enterotoxin B. The mature amino acid sequence of SEB contains ~~237~~ 239 amino acid residues and depicted in single-letter code comprises the following sequence:

ESQPDPKPDELHKSSKFTGLMENMKVLYDDNHVSAINVKSIDQFLYFDLIYSIKDTKLGNY
DNVRVEFKNKDLADKYKDKYVDVFGANYYYQCYFSKKTNDINSHQTDKRKTCMYGGVT
EHNGNQLDKYRSITVRVFEDGKNLLSFDVQTNKKKVTAQELDYLTRHYLVKNKKLYEFN
NSPYETGYIKFIENENSFWYDMMPAPGDKFDQSKYLMMYNDNKMVDSKDVKIEVYLTTK
KK (SEQ ID NO: 1). --

Please replace the paragraph beginning at line 20 on page 8 of the specification with the following amended paragraph:

-- an accordingly specified molecule wherein alteration is conducted at one or more residues from the string of contiguous residues defined herein as epitope region R1, R2 and R3:

R1: KFTGLMENMKVLYDDNHVSAI (SEQ ID NO: 2; amino acid residues 16-36 of SEQ ID NO: 1);

R2: QFLYFDLIYSIKDTKLGNYDNVRV (SEQ ID NO: 3; amino acid residues 43-66 of SEQ ID NO: 1);

R3: NKDLADKYKDKYVDVFGANYYYQCYFSKKTNDI (SEQ ID NO: 4; amino acid residues 70-102 of SEQ ID NO: 1). --

Please replace the paragraph beginning at line 26 on page 8 of the specification with the following amended paragraph:

-- an accordingly specified molecule wherein alteration is conducted at one or more residues from the string of contiguous residues defined herein as preferred epitope region R1a, R1b, R1c and comprising the sequence:

R1a KFTGLMENMKVLYDD (SEQ ID NO: 13; amino acid residues 16-30 of SEQ ID NO: 1),

R1b: GLMENMKVLYDDNHV (SEQ ID NO: 14; amino acid residues 19-33 of SEQ ID NO: 1),

R1c: ENMKVLYDDNHVSAI (SEQ ID NO: 15; amino acid residues 22-36 of SEQ ID NO: 1). --

Please replace the paragraph beginning at line 1 on page 9 of the specification with the following amended paragraph:

-- an accordingly specified molecule wherein alteration is conducted at one or more residues from the string of contiguous residues defined herein as preferred epitope region R2a and comprising the sequence SIKDTKLGNYDNVRV (SEQ ID NO: 25; amino acid residues 52-66 of SEQ ID NO: 1); --

Please replace the paragraph beginning at line 4 on page 9 of the specification with the following amended paragraph:

-- an accordingly specified molecule wherein alteration is conducted at one or more residues from the string of contiguous residues defined herein as preferred epitope region R3a and comprising the sequence DKYVDVFGANYYYQC (SEQ ID NO: 34; amino acid residues 79-93 of SEQ ID NO: 1); --

Please replace the paragraph beginning at line 11 on page 9 of the specification with the following amended paragraph:

-- a modified SEB molecule comprising the amino acid sequence of Formula I (SEQ ID NO:5):

X^0ESQPDPKPDELHKSSKFTGLX^1ENX^2KVLX^3DDNHVSAINVKSIDQFLYFDLIYSX^4KDTK X^5GNYDNVRVEFKNKDLADKYKDKX^6X^7DX^8X^9GANYYYQCYFSKKTNDINSHQTDKRKT CMYGGVTEHNGNQLDKYRSITVRVFEDGKNLLSFDVQTNKKKVTAQELDYLTRHYLVKN

KKLYEFNNSPYETGYIKFIENENSFWYDMMPAPGDKFDQSKYLMMYNDNKMVDSKDVKI EVYLTTKKK, wherein

X^0 is hydrogen or a targeting moiety such as an antibody, an antibody domain [Fab', $F(ab)_2$', scFv, Fc-domain], or another protein or polypeptide;

X^1 = A, G, P or M;

X^2 = A, G, P, or M;

X^3 = T, A, D, E, G, H, K N, P, Q, R, S, or Y;

X^4 = A, or I;

X^5 = H, or L;

X^6 = T, A, D, E, G, H, K N, P, Q, R, S, or Y;

X^7 = H, or V;

X^8 = A, P, G, or V;

X^9 = T, H, or F;

whereby simultaneously X^1 = M, X^2 = M, X^3 = Y, X^4 = Y, X^5 = L, X^6 = Y, X^7 = V, X^8 = V and X^9 = F are excluded. --

Please replace the paragraph beginning at line 22 on page 12 and continuing through line 22 on page 13 of the specification with the following amended paragraph:

-- According to the method, synthetic peptides are tested for their ability to evoke a proliferative response in human T-cells cultured *in vitro*. The T-cells are present within peripheral blood mononuclear cell (PBMC) layer readily obtainable by well known means from whole blood samples. Moreover the PBMC preparation contains physiological ratios of T-cells and antigen presenting cells and is therefore a good source of materials with which to conduct a surrogate immune reaction in vitro. The inventors have established that in the operation of such an assay, a stimulation index ~~closly~~ closely approaching or exceeding 2.0 is a useful measure of induced proliferation. The stimulation index (SI) is conventionally derived by division of the proliferation score (e.g. counts per minute of radioactivity if using for example ^{3}H-thymidine incorporation) measured to the test peptide by the score measured in cells not contacted with a test peptide. Peptides which evoke no response give SI = 1.0 although in practice SI values in the range 0.8 - 1.2 are unremarkable. A number of technical ~~proceedures~~ procedures can be inbuilt into the operation

of such assays in order to ensure confidence in the recorded scores. Typically all determinations are made at least in triplicate and the mean score may be computed. Where a computed SI =>2.0 individual scores of the triplicate can be examined for evidence of outlying data. Test peptides are contacted with cells in at least two different concentrations and the concentrations would typically span a minimum two-fold concentration difference. Such a concentration range provides an off-set to the kinetic dimension to the assay and is especially important where a single time point determination, for example at plus day 7, is being conducted. In some assays multiple time course determinations may be conducted but in any event these too would be made using peptide immunogen provided at a minimum of two different concentrations. Similarly the inclusion of control peptides for which there is expectation that the majority of PBMC donor samples will be responsive may be included in each assay plate. The influenza haemagglutinin peptide 307-309, sequence PKYVKQNTLKLA (SEQ ID NO: 6); and the *Chlamydia* HSP 60 peptide sequence KVVDQIKKISKPVQH (SEQ ID NO: 7) are particularly suitable control peptides although many other examples may be exploited. Assays should preferably also use a potent whole protein antigen such as hemocyanin from Keyhole Limpet to which all PBMC samples would be expected to exhibit an SI significantly greater than 2.0. --

Please replace Table 1 on page 15 of the specification with the following amended table:

Peptide ID #	SEQ ID NO:	Residue #*	Peptide Sequence	Epitope Region
P6	13	16	KFTGLMENMKVLYDD	R1a
P7	14	19	GLMENMKVLYDDNHV	R1b
P8	15	22	ENMKVLYDDNHVSAI	R1c
P18	25	52	SIKDTKLGNYDNVRV	R2a
P27	34	79	DKYVDVFGANYYYQC	R3a

Please replace the paragraph beginning at line 21 on page 15 and continuing through line 5 on page 16 of the specification with the following amended paragraph:

-- Epitope region [[R1a]] R1 is encompassed by peptides P6, P7 and P8 comprising the sequence KFTGLMENMKVLYDDNHVSAI (SEQ ID NO: 2). Note that for the [[R1a]] R1 epitope, peptides P6 and P8 are reactive each with two donors samples whereas the intervening peptide P7 is reactive with only one of the donors. In this instance the P7 reaction gave a particularly high SI score (8.1) and reactive sample is also reactive with P6 and P8. Owing to the phasing of each successive peptide in the sequence, it is possible that the same core nonamer sequence could be shared ([[i.e]] i.e., is common) between either 2 or 3 adjacent peptides. The exact phasing is dependent on proximity to the N-terminus and tied to the length of the peptides and number of "new" residues scanned by each successive increment of the sequence. In the case of the [[R1a]] R1 epitope, a number of overlapping MHC class II ligands could be identified (see FIGURE 1). --

Please replace the paragraph beginning at line 6 on page 16 of the specification with the following amended paragraph:

-- Epitope region [[R2]] R2a is encompassed by peptide P18 comprising the sequence SIKDTKLGNYDNVRV (SEQ ID NO: 25). --

Please replace the paragraph beginning at line 6 on page 16 of the specification with the following amended paragraph:

-- Epitope region [[R3]] R3a is encompassed by peptide P27 comprising the sequence DKYVDVFGANYYYQC (SEQ ID NO: 34). --

Please replace the paragraph beginning at line 23 on page 23 of the specification with the following amended paragraph:

-- ~~FIGURE 1~~ FIGURE 1 is a depiction of the MHC class II ligands identified within epitope region [[R1a]] R1. Ligands are identified using the *in silico* system of EXAMPLE 2. In this case the binding profile of 18 human DR allotypes are displayed as columns. The ligands detected are 13-mers and residue number 1 of each 13-mer is identified by a ~~coloured~~ colored block. The intensity of the binding interaction (High, Medium or Low) for each peptide with respect to each of the 18

allotypes is indicated according to the key displayed. Residues 16-35 of SEQ ID NO: 1 are shown vertically in the first column. --

Please replace the paragraph beginning at line 30 on page 23 and continuing through line 2 on page 24 of the specification with the following amended paragraph:

-- ~~FIGURE 2~~ FIGURE 2 is a depiction of the MHC class II ligands identified within epitope region [[R2]] R2a. Ligands are identified using the *in silico* system of EXAMPLE 2. In this case the binding profile of 18 human DR allotypes are displayed as columns. The ligands detected are 13-mers and residue number 1 of each 13-mer is identified by a ~~coloured~~ colored block. The intensity of the binding interaction (High , Medium or Low) for each peptide with respect to each of the 18 allotypes is indicated according to the key displayed. SEQ ID NO: 25 (residues 52-66 of SEQ ID NO: 1) is shown vertically in the first column. --

Please replace the paragraph beginning at line 10 on page 23 of the specification with the following amended paragraph:

-- ~~FIGURE 3~~ FIGURE 3 is a depiction of the MHC class II ligands identified within epitope region [[R3]] R3a. Ligands are identified using the *in silico* system of EXAMPLE 2. In this case the binding profile of 18 human DR allotypes are displayed as columns. The ligands detected are 13-mers and residue number 1 of each 13-mer is identified by a ~~coloured~~ colored block. The intensity of the binding interaction (High , Medium or Low) for each peptide with respect to each of the 18 allotypes is indicated according to the key displayed. SEQ ID NO: 34 (residues 79-93 of SEQ ID NO: 1) is shown vertically in the first column. --

Please replace the paragraph beginning at line 24 on page 25 of the specification with the following amended paragraph:

-- Each peptide was screened individually against PBMC's isolated from 20 naïve donors. Two control peptides that have previously been shown to be immunogenic and a potent non-recall antigen KLH were used in each donor assay. The control antigens used in this study were Flu haemagglutinin 307-319 (sequence: PKYVKQNTLKLAT; SEQ ID NO: 6); ~~Chlamydia~~ *Chlamydia* HSP 60 peptide (sequence: KVVDQIKKISKPVQH; SEQ ID NO: 7) and Keyhole Limpet

hemocyanin. The tissue types for all PBMC samples were assayed using a commercially available reagent system (Dynal, Wirral, UK). Assays were conducted in accordance with the suppliers recommended protocols and standard ancillary reagents and agarose electrophoresis systems. --

Please replace Table 2 beginning on page 26 of the specification with the following amended table:

Peptide ID #	SEQ ID NO:	SEB; 15 mer peptide sequence	Residue #
P1	8	ESQPDPKPDELHKSS	1
P2	9	PDPKPDELHKSSKFT	4
P3	10	KPDELHKSSKFTGLM	7
P4	11	ELHKSSKFTGLMENM	10
P5	12	KSSKFTGLMENMKVL	13
P6	13	KFTGLMENMKVLYDD	16
P7	14	GLMENMKVLYDDNHV	19
P8	15	ENMKVLYDDNHVSAI	22
P9	16	KVLYDDNHVSAINVK	25
P10	17	YDDNHVSAINVKSID	28
P11	18	NHVSAINVKSIDQFL	31
P12	19	SAINVKSIDQFLYFD	34
P13	20	NVKSIDQFLYFDLIY	37
P14	21	SIDQFLYFDLIYSIK	40
P15	22	QFLYFDLIYSIKDTK	43
P16	23	YFDLIYSIKDTKLGN	46
P17	24	LIYSIKDTKLGNYDN	49
P18	25	SIKDTKLGNYDNVRV	52
P19	26	DTKLGNYDNVRVEFK	55
P20	27	LGNYDNVRVEFKNKD	58
P21	28	YDNVRVEFKNKDLAD	61
P22	29	VRVEFKNKDLADKYK	64
P23	30	EFKNKDLADKYKDKY	67
P24	31	NKDLADKYKDKYVDV	70
P25	32	LADKYKDKYVDVFGA	73
P26	33	KYKDKYVDVFGANYY	76
P27	34	DKYVDVFGANYYYQC	79

Peptide ID #	SEQ ID NO:	SEB; 15 mer peptide sequence	Residue #
P28	35	VDVFGANYYYQCYFS	82
P29	36	FGANYYYQCYFSKKT	85
P30	37	NYYYQCYFSKKTNDI	88
P31	38	YQCYFSKKTNDINSH	91
P32	39	YFSKKTNDINSHQTD	94
P33	40	KKTNDINSHQTDKRK	97
P34	41	NDINSHQTDKRKTCM	100
P35	42	NSHQTDKRKTCMYGG	103
P36	43	QTDKRKTCMYGGVTE	106
P37	44	KRKTCMYGGVTEHNG	109
P38	45	TCMYGGVTEHNGNQL	112
P39	46	YGGVTEHNGNQLDKY	115
P40	47	VTEHNGNQLDKYRSI	118
P41	48	HNGNQLDKYRSITVR	121
P42	49	NQLDKYRSITVRVFE	124
P43	50	DKYRSITVRVFEDGK	127
P44	51	RSITVRVFEDGKNLL	130
P45	52	TVRVFEDGKNLLSFD	133
P46	53	VFEDGKNLLSFDVQT	136
P47	54	DGKNLLSFDVQTNKK	139
P48	55	NLLSFDVQTNKKKVT	142
P49	56	SFDVQTNKKKVTAQE	145
P50	57	VQTNKKKVTAQELDY	148
P51	58	NKKKVTAQELDYLTR	151
P52	59	KVTAQELDYLTRHYL	154
P53	60	AQELDYLTRHYLVKN	157
P54	61	LDYLTRHYLVKNKKL	160
P55	62	LTRHYLVKNKKLYEF	163
P56	63	HYLVKNKKLYEFNNS	166
P57	64	VKNKKLYEFNNSPYE	169
P58	65	KKLYEFNNSPYETGY	172
P59	66	YEFNNSPYETGYIKF	175
P60	67	NNSPYETGYIKFIEN	178
P61	68	PYETGYIKFIENENS	181

Peptide ID #	SEQ ID NO:	SEB; 15 mer peptide sequence	Residue #
P62	69	TGYIKFIENENSFWY	184
P63	70	IKFIENENSFWYDMM	187
P64	71	IENENSFWYDMMPAP	190
P65	72	ENSFWYDMMPAPGDK	193
P66	73	FWYDMMPAPGDKFDQ	196
P67	74	DMMPAPGDKFDQSKY	199
P68	75	PAPGDKFDQSKYLMM	202
P69	76	GDKFDQSKYLMMYND	205
P70	77	FDQSKYLMMYNDNKM	208
P71	78	SKYLMMYNDNKMVDS	211
P72	79	LMMYNDNKMVDSKDV	214
P73	80	YNDNKMVDSKDVKIE	217
P74	81	NKMVDSKDVKIEVYL	220
P75	82	VDSKDVKIEVYLTTK	223
P76	83	KDVKIEVYLTTKKK	226
P77	84	KIEVYLTTKKK	229

Please replace Table 3 on page 29 of the specification with the following amended table:

Peptide ID #	SEQ ID NO:	Peptide Sequence	SI per responsive sample*	Responsive Allotypes
P6	13	KFTGLMENMKVLYDD	3.4, 2.1	DRB1*04, DRB4*01; DRB1*07, DRB1*11, DRB3
P7	14	GLMENMKVLYDDNHV	8.1	DRB1*04, DRB4*01
P8	15	ENMKVLYDDNHVSAI	4.4 3.1	DRB1*04, DRB4*01; DRB1*07, DRB1*09, DRB4*01
P18	25	SIKDTKLGNYDNVRV	2.2 5.1 2.0	DRB1*04, DRB4*01; DRB1*07, DRB1*09, DRB1*12, DRB1*15, DRB3, DRB5
P27	34	DKYVDVFGANYYYQC	2.3 5.3 2.5	DRB1*04, DRB4*01; DRB1*07, DRB1*09, DRB1*07, DRB1*11, DRB3